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Physiologic Effects of Steroid Hormones and Postmenopausal Hormone Replacement on the Female Breast and Breast Cancer Risk

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It is no mystery that hormones influence both normal breast growth and development as well as breast tumorigenesis. What defines the influences of hormones on the female breast is, however, complex and poorly understood by most clinicians treating breast diseases. In particular, there has been a long-standing concern about breast cancer risk in women who use exogenous hormones.

The first part of this in-depth review of the topic addresses some of the salient background information necessary for a solid understanding of normal breast growth and development, as well as cancer etiology. Examined in the second part are several of the controversies regarding the benefits and risks of exogenous hormone use in postmenopausal women.

PART I

Cellular Action of Hormones

The action of steroid hormones, including estrogen and progesterone, on breast cells is summarized in Figures 1 and 2, as well as Table 1. Steroid hormones present in plasma enter breast cells through both passive and active mechanisms of uptake. Estrogen upregulates the production of not only its own receptor, but also progesterone receptors. Progesterone has the opposite effect, downregulating both progesterone and estrogen receptors. The receptor status of normal breast tissue depends on the phase of the menstrual cycle. Estrogen receptor-positive cells are found only in the follicular phase of the menstrual cycle. However, tumor cells are either positive or negative for estrogen receptor, irrespective of the phase of the menstrual cycle.

Once in the cell, hormones bind to both cytoplasmic and nuclear hormone receptors, forming a hormone–receptor complex. The extent to which estrogen binds to its receptor is influenced by the concentration of estrogen as well as the type of estrogen present. Estradiol has the strongest affinity for the estrogen receptor, compared with estrone and estriol. The receptor itself is composed of four distinct domains (Fig. 3): domains for ligand binding and DNA binding, a hinge region, and a regulatory domain.[1]

Estrogen–receptor complexes become activated by a conformational change and can then bind with a DNA target sequence, stimulating transcription of messenger RNA and protein synthesis. In response to estrogen-induced genes, the production of growth factors is increased (*e.g.*, transforming growth factor alpha and epidermal growth factor), whereas the production of growth inhibitors is decreased (*e.g.*, transforming growth factor beta).[2] The protein products of the *myc, ras*, and *fos* oncogenes are also produced in response to activation of the estrogen DNA target sequence. This may, in theory, partially explain the abnormal growth of some breast tumors in response to hormonal stimulation. Oncogenes may also bypass normal control mechanisms for estrogen-induced proliferation and independently stimulate cell growth through direct effects on the estrogen DNA target sequence or coexpression of growth factors and growth factor receptors.

Some oncogene protein products, such as those of HER-2/*neu*, share significant homology with receptors for growth factors; others, such as PRAD-1, amplify the production of cell cycle regulatory proteins called cyclins.[3,4] By mimicking growth factor receptors, oncogene protein products can increase a cell's sensitivity to normally circulating factors and encourage abnormal growth by providing a growth advantage in these cells. Cyclin amplification allows cells to continue through the cycle unchecked, thus providing yet another pathway of escape from normal growth control. The PRAD-1 oncogene, for example, amplifies the production of cyclin D, an essential component of the G_1 phase of the cell cycle.[5,6] Allowing these cells to override normal safeguards governing the G_1/S transition may result in uncontrolled growth and tumorigenesis. The concepts involving bypass of the normal estrogen response are important, particularly when we consider hormone replacement therapy in women who are at high risk for the development of breast cancer or who have had a prior diagnosis of breast cancer.

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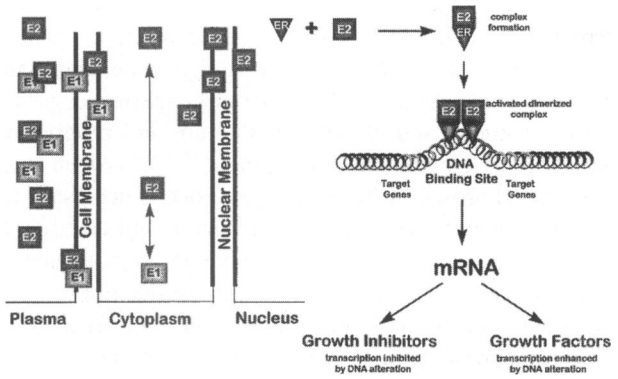

Figure 1. Cellular action of estrogen. Estrogen moves from the plasma to the cell by both passive and active mechanisms of uptake. Once in the cell, estrogen binds to both cytoplasmic and nuclear hormone receptors. Estrone (E1) is converted to estradiol (E2) within the cytoplasm. Estradiol has the strongest affinity for the estrogen receptor (ER). Both estrogen and progesterone receptor levels are increased in the presence of estrogen. Hormone–receptor complexes dimerize and undergo conformational changes that result in activation of the complex and binding to DNA target sequences. Ultimately, proteins such as growth factors are synthesized. Growth inhibitor production is decreased in response to estrogen stimulation.

Influence of Estrogen and Progesterone on Breast Growth

Estrogen-induced proliferation has been postulated to correlate with a greater likelihood of a random genetic error.[7,8] In addition, proliferating cells are more susceptible to carcinogenic and mitogenic influences than are quiescent cells.

Korenman,[9] in 1980, suggested that the endocrine environment of the breast influenced susceptibility to cancer but did not itself cause cancer. His argument was that the hormonal environment of the breast was necessary but not sufficient to cause cancer. He coined the term "estrogen window," which refers to periods of unopposed estrogen.

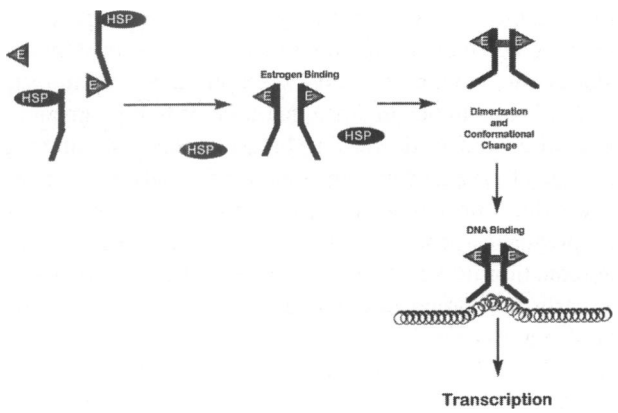

Figure 2. Estrogen–receptor complex formation and DNA binding. Estrogen binds to its receptor, releasing heat-shock protein (HSP). After the estrogen–monomer complex is formed, the complex dimerizes and undergoes conformational change. This change in shape allows DNA binding, transcription, and protein synthesis.

Table 1. SUMMARY OF HORMONAL ACTION ON BREAST CELLS

Estrogen	Progesterone
Stimulates ductal growth	Stimulates alveolar growth
Proliferative effect	Both proliferative and anti-proliferative effects
Highest during follicular phase	Highest during leuteal phase
Increases estrogen and progesterone receptors	Decreases estrogen and progesterone receptors
Increased growth factor production	Induces differentiation

Several correlates form the basis of this hypothesis, including the following:

- Human breast cancer is induced by carcinogens in a susceptible mammary gland.
- Unopposed estrogenic stimulation is the most favorable state for induction.
- There is a long latency between induction of tumor and clinical expression.
- The duration of the estrogen window determines risk.
- Inducibility declines with the establishment of normal ovulatory menses and becomes very low during pregnancy.

The window is "open" twice in a woman's life. The first, during adolescence (Tanner stage 2), represents the time from menarche to ovulation. The beginning of menses does not correlate with the beginning of normal ovulatory cycles. This period of anovulation lasts an average of 2.3 years, but can last up to 6 years.[10] The second time during which a women is exposed to unopposed estrogen is in the perimenopause. Again, the cycles are anovulatory. The duration of perimenopause is variable, however, being greatest for women with late rather than early menopause. This may account for the finding that late menopause elevates a woman's risk for the development of breast cancer. Extension of the perimenopause with exogenous hormones would lengthen the second "open window" phase of a woman's life and, based on Korenman's hypothesis, would increase the breast cancer risk by lengthening the duration of estrogen exposure in these women, thereby providing a cancer-supporting endocrine environment.

Interesting observations from Japan documented the incidence of breast cancer among women exposed to radiation after the atomic bomb blasts at Hiroshima and Nagasaki. The incidence of breast cancer was highest among women who were either adolescent or perimenopausal at the time of

Figure 3. Four functional domains of the estrogen receptor.

radiation exposure.[11] Similar findings were documented in women who underwent repeated fluoroscopic examinations for tuberculosis.[12] This type of information seems to point to the significance of the hormonal milieu of the breast with respect to susceptibility to carcinogens.

Using Korenman's hypothesis, we can broadly define the known risk factors for breast cancer as those that prolong the "open window." Theories that emphasize the importance of unopposed estrogen and increased breast cancer risk are bolstered by the finding that estrogen levels in breast tissue are a full order of magnitude greater than levels in plasma, although estrogen levels in breast tumor tissue do not correlate with plasma levels of estrogen.[13,14] Surely, then, estrogen must be an influential and essential hormone to breast growth and tumorigenesis.

The impact of the hormonal milieu is not evident in genetically at-risk women (*e.g.*, those with BRCA-1 or other genetic aberrations). Further work will be needed to ascertain how models such as that proposed by Korenman would enhance or be excluded by the ever-expanding knowledge base regarding the genetics of breast cancer. These types of hypotheses may also influence our understanding of growth factor and growth factor receptor aberrations such as the HER-2/*neu* homology discussed above. Finally, the impact of the hormonal milieu on cell cycle abnormalities also needs to be illustrated more fully.

The second major hormone affecting the breast is progesterone. This hormone increases mitotic activity, again making cells more susceptible to random genetic errors and to the influences of carcinogens. Progesterone levels are highest during the luteal phase of the menstrual cycle. The argument for progesterone's role in breast cancer development centers around the known risk factors of early menarche and late menopause. With more total ovulatory cycles (thus, more luteal phases) in a lifetime, the odds of a random genetic error are increased.

Studies on human cancer cells have been contradictory: both proliferative and antiproliferative effects of progestational agents have been observed in the laboratory setting. In one study, estrogen-stimulated growth of normal human breast cells, obtained from reduction mammoplasty specimens, was terminated by adding progestin to the culture medium.[15] A similar study treated normal breast cells with estrogen until cellular proliferation was induced. When progestin was added to the growing cells, cellular expansion was abrogated and the cells underwent differentiation.[16] The therapeutic implications from data such as these are uncertain. However, it has been suggested that progestin may be advantageous when added to estrogen replacement therapy.[17]

Menarche

Menarche marks the onset of sex steroid hormone production. It is during this time that mitotic activity is prominent, and the developing breast is thus susceptible to carcinogenic influences. Under the influence of sex steroid hormones (in addition to insulin, growth hormone, prolactin, epidermal growth factor, cortisol, thyroxine, and many others), an endocrinologically intact girl experiences proliferation of ductal and alveolar epithelium and progressive normal breast growth and development.[18,19] Estrogen stimulates ductal growth, whereas progesterone is necessary for alveolar growth.[20] The addition of insulin and cortisol, as well as prolactin, is necessary for alveolar cells to mature into milk-producing cells. The majority of ductal proliferation occurs during the luteal phase of the menstrual cycle. During this phase, there is an increase in the number of cells per terminal duct and in the number of terminal ducts per lobular unit. The effects of estrogen and the normal luteal phase on the terminal duct lobular unit are important because most breast cancers are ductal carcinomas and originate in the terminal duct lobular unit.

The concept that all hormones, not just estrogen and progesterone, are required for breast growth and development is critical because the influences of estrogen and progesterone on the breast and breast tumorigenesis are complex. Clearly, there are intricate interactions between hormones that have significant effects on target tissue. The notion that estrogen plus receptor leads to proliferation and the development of cancer is overly simplistic and probably naïve. As stated above, the finding that early menarche increases the risk for breast carcinogenesis may be explained by two closely related theories. First, early menarche would result in more total ovulatory cycles in a lifetime and, thus, a greater odds ratio of sustaining a genetic error.[21,22] Second, unopposed estrogen exposure as a result of anovulatory cycles during an early menarche may also heighten breast cancer risk.

Pregnancy

During pregnancy, mammary cells are exposed to extremely high levels of circulating hormones. The hormonal milieu not only induces proliferation, but also results in a differentiation of the mammary gland in the latter portion of the first pregnancy. Differentiation of omnipotent stem cells reduces the number of cells susceptible to carcinogenic stimuli. Most studies indicate that time of first pregnancy is most influential in decreasing breast cancer risk, although subsequent pregnancies may enhance this protective effect. In addition, most women have ovulatory cycles after the first pregnancy. These two factors may account for most of the reduction in breast cancer risk after the first pregnancy. An early first pregnancy would afford not only protection but also a lesser amount of time when the breast would be exposed to a hormonally susceptible atmosphere.

A Norwegian study of more than 800,000 women demonstrated a short-term increase in breast cancer risk, peaking at 3 to 4 years postpartum, followed by a long-term decrease in breast cancer risk.[23] Although that study demonstrated a protective effect during the 9 months of pregnancy itself, the

data must be interpreted with caution because of the way the study was performed. Pregnancies were identified by a registry of live births. Women in Norway who are diagnosed with breast cancer during pregnancy or who become pregnant after the diagnosis of breast cancer are encouraged to have abortions; therefore, these women would have been automatically excluded from the study population. Thus, the effects of the 9 months of pregnancy itself cannot be proved from this report.

Several studies have examined the prognostic effect of pregnancy after the diagnosis of breast cancer.[24–30] The basic hypothesis underlying each study was that the hormonal environment of pregnancy would decrease survival by enhancing the growth of tumor cells. This has not proved to be the case. From the results of these trials, there appears to be no adverse effect of pregnancy on breast cancer survival or recurrence. The observation that pregnant women have more aggressive disease appears to reflect the independent risk factor of young age in this group of patients and is not attributable to pregnancy.[31] Pregnant women with breast cancer who are matched for age and stage of disease have survival and recurrence rates similar to those of nonpregnant women.[32–34]

Critics of studies regarding pregnancy and breast cancer risk point out that most women were asked to wait 2 years after breast cancer diagnosis and treatment before becoming pregnant. This may have biased the data to include only women at low risk for recurrence. However, one report of women who conceived within 6 months of cancer treatment demonstrated survival rates similar to those of controls.[35]

Abortion and Breast Cancer Risk

The effect of abortion on breast cancer risk has been argued for many years. The premise was that induced abortion would increase breast cancer risk based on the presumption that interruption of pregnancy resulted in the proliferation of mammary cells without allowing terminal differentiation of those cells. The data have so far been conflicting, and the studies have been small or poorly controlled. A recent Danish study, however, seems to have addressed this issue in a statistically significant and well-designed manner.[36] Representing 371,000 abortions, 281,000 women were studied. Overall, there was no increased risk of breast cancer among women who had abortions, compared with controls.

Interestingly, gestational age did seem to make a difference in breast cancer risk. Women who underwent induced abortions at less than 7 weeks gestation had a lower risk for breast cancer development; those who underwent induced abortions at 12 weeks or greater gestation had an increased risk for breast cancer development. Two theories may explain this dichotomy. One is that women who had abortions after 12 weeks gestation were exposed to proliferative hormones for longer periods of time without having the benefit of terminal differentiation. The other is that the reasons for having the abortions may have been different at different gestational ages. Women undergoing early abortions may have done so because they represented truly unwanted pregnancies in a group of women representative of the overall population of Denmark. However, women who underwent late abortions may have done so because they were encouraged to do so, either because they had been diagnosed with breast cancer in the past or because they were diagnosed with breast cancer during the recorded pregnancy. Therefore, there may have been a disproportionate number of high-risk women in the group undergoing later abortions than in the group undergoing early abortions. The study design does not allow for analysis of these types of differences and, thus, neither theory is proved.

Obesity and Breast Cancer Risk

Obesity increases breast cancer risk in postmenopausal women.[37] Adrenal androstenedione is converted to estrone in adipose tissue. The increased conversion of adrenal steroids to estrogens leads to higher levels of unopposed estrogens. In addition, estrogen receptor levels are higher in obese women, perhaps making their cells more responsive to these circulating estrogens by the formation of more estrogen–receptor complexes.[38] The end result is, again, a greater number of mitoses induced by persistent estrogen stimulation and an increased odds ratio of sustaining a random genetic error, leading to enhanced susceptibility to carcinogenic stimuli. Obesity in premenopausal women has been associated with a decreased risk for breast cancer.[39,40] This contrast in breast cancer risk among premenopausal and postmenopausal obese women is not clearly explained.

Oral Contraceptive Use

Oral contraceptives have been widely available for use in this country since the 1960s. Because these formulations have been available for only a relatively short time, the lifetime risks associated with oral contraceptive use are only now becoming evident. There have been many studies regarding the use of oral contraceptives and breast cancer risk. Overall, the studies vary, some demonstrating increased risk and others demonstrating decreased risk.

American and European studies are difficult to compare because the European studies include women who use estradiol, a synthetic estrogen that has been shown to increase breast cancer risk. American studies include only formulations containing conjugated estrogens derived from horse urine, which have not been demonstrated conclusively to correlate with increased breast cancer risk. In addition, the doses used in some European studies are twice those used in the United States. Finally, the reasons for prescribing exogenous hormones vary between the continents. In Europe, women receive hormones for birth control and for relief of menopausal symptoms. In the United States, hormones are prescribed for these two reasons, as well as to control

menstrual cycles, prevent cardiovascular disease, and treat osteoporosis.

The Cancer and Steroid Hormone Study by the Centers for Disease Control was a large study to address the issue of breast cancer risk and oral contraceptive use.[41] The study compared 4711 women with breast cancer with 4676 women without breast cancer. The number of women who used oral contraceptives was approximately 50% in the two groups. The authors concluded that oral contraceptive use did not increase the risk of breast cancer (RR = 1). Even 15 years or more of oral contraceptive use did not increase the risk for the development of breast cancer (RR = 0.6). In addition, subgroup analysis demonstrated no increased risk of breast cancer based on menopausal status, family history, use before first-term pregnancy, or type of formulation used.

Because of age-specific differences in breast cancer risk factors, the data from the Cancer and Steroid Hormone Study were reexamined to assess for breast cancer risk at varying patient ages. Women diagnosed with breast cancer or interviewed at age 20 to 34 and who used oral contraceptives had a slightly higher odds ratio for breast cancer compared with those who did not use oral contraceptives, (OR = 1.4, 95% CI 1.0 to 2.1). For women age 35 to 44, there was no association between oral contraceptive use and breast cancer risk. Women age 45 to 54 had a slightly decreased risk of breast cancer (OR = 0.9, 95% CI 0.8 to 1).[42] These data seem to indicate that although there is no overall increase in breast cancer risk related to oral contraceptive use, there may be a slight elevation of risk in very young women.

Exogenous Hormones and Benign Breast Disease

Physicians and scientists have postulated that the use of exogenous hormones by women with benign breast disease would increase the risk for the later development of breast cancer, based on the theories discussed above. In a large series, Dupont et al.[43] examined more than 10,000 breast biopsy specimens to assess the effect of exogenous hormones on benign diseases of the breast, including benign proliferative diseases of the breast. They found that breast cancer risk was not increased—in fact, it was decreased—in women who used hormones compared with those who did not use hormones.

Women with atypical hyperplasia also had a decreased risk for breast cancer if hormones were used compared to when hormones were not used. Atypical hyperplasia is a risk factor for breast cancer. The authors concluded that the increased relative risk for the development of breast cancer could be lowered from 4.5 to 3 by using hormones. This difference was not statistically significant, however ($p = 0.3$). Perhaps their conclusion should be modified slightly to state that the use of exogenous hormones does not increase the relative risk for breast cancer in women with benign breast disease, including atypical hyperplasia. Although this study had some shortcomings, it demonstrated categorically that the use of exogenous hormones does not increase the risk for breast cancer in women with benign breast disease, including proliferative diseases and atypical hyperplasia. The Cancer and Steroid Hormone Study corroborated these findings.

Exogenous Hormones, Alcohol, and Breast Cancer Risk

Several studies have linked exogenous hormone use in conjunction with alcohol consumption with an increased risk for breast cancer. The Nurses' Health Study noted that hormone use in conjunction with alcohol intake was associated with an increased breast cancer risk. The authors unexpectedly found a relative risk of 1.56 (95% CI 1.2 to 2) among women who used both alcohol and hormones compared with women who used hormones but did not drink alcohol.

Gapstur and associates[44,45] demonstrated, in addition to an increased risk of breast cancer, an association between alcohol consumption and breast cancer hormone receptor status. The relative risk for having tumors negative for both estrogen and progesterone receptor was 2.6 for women who consumed alcohol and used hormones compared with women who used hormones but did not drink alcohol.

Exogenous Hormone Use and Mammographic Parenchymal Patterns

Because of the proliferative influence of estrogen on breast parenchyma, there has been some concern regarding the effects that hormone replacement therapy (HRT) may have on mammographic patterns, interpretation, and threshold for the detection of cancers. Screening mammography is one of the most effective means of detecting early breast cancer and has decreased the breast cancer mortality rate in women older than age 50. There has been concern that HRT may decrease the screening efficacy of mammography by lowering sensitivity and specificity. These effects could potentially increase the breast cancer mortality rate by reducing the detection of early breast cancers.

A study by Bland et al.[46] reviewed 405 postmenopausal women, mean age 59.7 years, to assess the effects of exogenous hormone use on mammographic parenchymal patterns and interpretation. Women were classified as symptomatic if they had a mass or thickening; mastalgia; macrocystic changes; or nipple discharge. The women were then divided into four groups: asymptomatic and no hormones; symptomatic and no hormones; asymptomatic using hormones; and symptomatic using hormones. Follow-up ranged from 3.5 to 28.5 years. The dominant parenchymal pattern for each group was then mammographically determined. Although women using HRT demonstrated a more glandular pattern, this was noted to be within the range of interpretation error of the mammographer. Five cancers

were detected in 152 women using hormones, whereas 7 cancers were detected in 124 women not using hormones. Long-term estrogen replacement did not alter mammographic patterns in that study. These data suggest that the use of exogenous hormones does not interfere with mammographic interpretation or cancer detection.

Laya et al.[47] came to the opposite conclusion in a retrospective cohort study reviewing sensitivity and specificity of mammography in postmenopausal women using exogenous hormones, compared with those who had used them in the past or who had never used them. They included 8779 women who were part of a health maintenance organization in Washington state. Using two-view mammography, cancer screening was performed between 1988 and 1993. Women diagnosed with breast cancer were identified through a regional cancer registry, and risk ratios for false-positive and false-negative mammography results were then calculated. The authors found that both the specificity and the sensitivity of screening mammograms were decreased among current users of exogenous hormones compared with women who had never used them. The relative risk for a false-positive result was 1.33 (95% CI 1.15 to 1.54, $p < 0.001$) among current users compared with 1 (95% CI 0.87 to 1.15) for women who had never used them. Mammographic specificity was 86%, 86%, and 82%, respectively, for never, past, and current users of exogenous hormones. The relative risk for a false-negative mammography result was 5.23 (95% CI 1.09 to 25.02) for current users compared with those who had never used them. Mammographic sensitivity was 94%, 94%, and 69%, respectively, for never, past, and current users.

The pitfalls of this study lie in the use of a retrospective cohort. In addition, the small number of cancer cases resulted in a wide 95% confidence interval for sensitivity. Also, because of the sample size, sensitivity could not be adjusted for important confounders. Patients were identified as users or nonusers of hormones based on questionnaires, and this may have resulted in erroneous classification or grouping of patients. Effects of the duration of hormone use could not be analyzed using these data.

In light of these criticisms, the data suggest that mammographic screening may have an increased false-positive rate among hormone users, resulting in decreased specificity. The decreased sensitivity, however, may not be significant because of the drawbacks noted above. Therefore, although cost may be increased as a result of false-positive mammography results, the effects of hormone use on sensitivity are not clear. This study cannot answer whether or not early cancers were truly missed by screening mammography in women using HRT.

Summary

The hormonal environment of the breast is clearly influential with regard to normal growth and development as well as cancer risk. Nonetheless, it appears that for most women, the risk/benefit ratio supports the use of exogenous hormones. There remain several groups of women, however, for whom the data are not as compelling.

PART II

This part of the review focuses on the use of exogenous hormones in postmenopausal women and the current controversies surrounding this topic.

During the menopause, sex steroid hormone levels drop, leading to variable and anovulatory menstrual cycles in the perimenopause. Women who undergo late menopause have a greater perimenopausal exposure to unopposed estrogen and more variability with regard to anovulatory cycles than do women who undergo earlier menopause. This may explain the increased breast cancer risk among women who undergo late menopause.

The menopause has effects on bone density, cardiovascular health, vasomotor stability, and the urogenital tract, in addition to its effects on breast tissue. The risk of osteoporosis is significant in postmenopausal women. Between 25% and 44% of women in this age group have spontaneous fractures, including vertebral fractures.[48,49] There is a precipitous decline in bone density beginning in the perimenopause and continuing thereafter because of a predominance of osteoclastic activity. The risk for death and complications related to osteoporosis represents a serious public health concern. In addition, although we are focusing on breast cancer risk, we must keep in mind that the leading cause of death for women in the United States is not breast cancer, but cardiovascular disease. The use of preventive or protective medications that can reduce this risk is an imperative public health issue, and certainly one worthy of strong consideration in most women.

Risk/Benefit Analysis in Postmenopausal Hormone Replacement

As mentioned earlier, there are significant benefits to HRT in postmenopausal women. The ability to lower a woman's risk for cardiovascular disease is not trivial. Many studies demonstrate a clear decrease in cardiovascular disease among women who take exogenous hormones compared with matched controls.[50–52] The Nurses' Health Study demonstrated that women who used HRT had a 50% decrease in the rate of myocardial infarctions and a 25% reduction in cardiovascular deaths, without an associated increase in stroke risk, compared with women who did not use HRT. The cardioprotective effect of estrogens is the result partly of improvements in the lipid and cholesterol profile and partly of augmentation of blood flow to the myocardium. Estrogen receptors have been found in the smooth muscle of the coronary arteries; by stimulating endothelium-derived relaxing factor, estrogen dilates the coronary arteries.[53] A recent study demonstrated that con-

jugated estrogens used with or without progesterone reduced plasminogen-activator inhibitor type 1 by approximately 50%. This finding translates into enhanced fibrinolysis with an attendant lowered risk for atherosclerosis and coronary artery disease in postmenopausal women.[54]

Estrogen has been used both for the prophylaxis and therapy of osteoporosis. Primarily trabecular bone is lost during the menopause, but cortical bone density also diminishes. Trabecular bone is lost rapidly beginning at the perimenopause, and both cortical bone and trabecular bone continue to decline steadily throughout the menopausal years.[55–57] Bone density is maintained and can even be improved when estrogen is added to a regimen of calcium replacement and exercise.[58–60]

For most women, the greatest benefit of HRT centers around quality-of-life issues. Relief of menopausal symptoms is perhaps the most common reason why women request HRT. Hot flashes and symptoms of urogenital atrophy (*e.g.*, urinary urgency, dyspareunia) can be relieved with HRT.[61–65] Psychic disturbances such as depression and insomnia can also be relieved with HRT. Perhaps secondary to the relief of these symptoms, many women also state that they have improved concentration when using HRT than when they are not.

The drawbacks to HRT include return of menstruation and premenstrual symptoms. In addition, there are changes in glucose homeostasis as well as increased blood coagulability, with a resultant increase in the incidence of superficial phlebitis and increased susceptibility to deep vein thrombosis. Endometrial cancer risk is increased four- to sevenfold when exogenous estrogens are used.[66,67] This increased risk can be countered, however, by the addition of progesterone to the estrogen replacement regimen.[68] Finally, there is controversy surrounding a possible increased risk for the development of breast cancer.

In assessing the benefits of HRT versus the risk of breast cancer, one must consider the overall impact of HRT on the mortality rate of older women. There are significant decreases in death from cardiovascular disease and osteoporosis in women who use exogenous hormones. Whether or not there is attenuation of the cardioprotective effect when progesterone is added to estrogen replacement is controversial. One large study demonstrated that progesterone did not attenuate this effect.[69] The death rate from endometrial cancer returns to baseline with the addition of progesterone. The result is a significant decrease in the mortality rate when HRT is used in postmenopausal women.

A recent study used a decision analysis model to link risk factors to disease incidence and to estimate lifetime risks for coronary artery disease, breast cancer, hip fracture resulting from osteoporosis, and endometrial cancer.[70] The impact of HRT was then estimated from epidemiologic studies. A mathematical model was then created to determine the effect of HRT on life expectancy in postmenopausal women with varying risk profiles.

For most women, the gains of HRT outweighed any risks

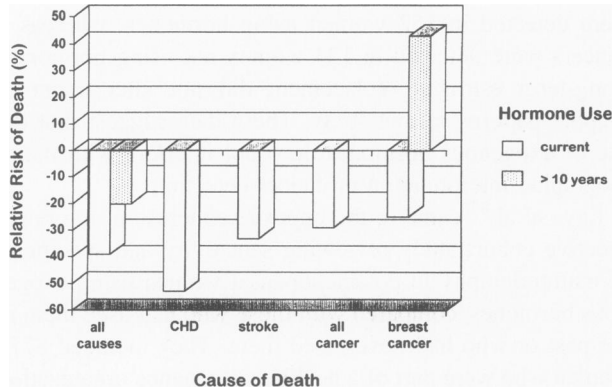

Figure 4. Summary of the Nurses' Health Study data on mortality rates and postmenopausal hormone therapy. The risk of death is decreased most in women at high risk for cardiovascular disease who are currently using hormone replacement. Long-term hormone use provides an overall improvement in survival of 20%, although the breast cancer rate increases 43%. (Adapted from Grodstein et al.[71])

associated with its use. For women at high risk for breast cancer, the presence of just one risk factor for coronary artery disease favored the use of hormone replacement in extending life expectancy. The only group of women who would not benefit by HRT based on this decision analysis model are women at greatest risk for breast cancer and lowest risk for coronary artery disease. The data suggest that more comprehensive use of HRT should be considered in postmenopausal women.

As with all mathematical models attempting to assess individual risk based on population studies, the drawbacks to this study are that assumptions were made and included in the model. Some assumptions also introduced selection bias. However, the authors consistently used calculations that would underestimate the benefits of HRT and used only diseases for which there was convincing evidence of the impact of HRT. This deliberate underestimation of the beneficial effects of HRT further enhances the conclusion that most women will live longer if they use exogenous hormones than if they do not.

The most recent follow-up from the Nurses' Health Study[71] assessed postmenopausal HRT and mortality rates. The data demonstrated that current hormone users had an overall decrease in mortality of 37% compared with never users. The reduction in the risk of death was greatest, 49%, for women at high risk for cardiovascular disease who were current users of hormones. Mortality decreased least, 11%, among hormone users at low risk for cardiovascular disease. For women using hormones for 10 or more years, there was a more modest, 20%, overall decreased risk of death. This is less than the 37% overall reduction in death among women using hormones for less than 10 years (Fig. 4). The decrease in survival benefit was the result of an increase, 43%, in deaths from breast cancer. The increased death rate from breast cancer, despite the overall 20% improvement in survival, is difficult to explain. However, it may be explained by the fact that these women were living longer and reach-

Figure 5. Effect of estrogen on the risk of endometrial and breast cancer. The relative risk of endometrial cancer, but not of breast cancer, rises progressively with increasing time of exposure to unopposed estrogen. (From Harlap.[72])

ing an age when breast cancer is more prevalent. This study appears to corroborate the findings of the previously mentioned report, and may also demonstrate that short-term HRT is beneficial in a broad group of women. HRT started after the menopause, rather than in the perimenopause, may prove to be most beneficial for most women. This may provide all the benefits of HRT while minimizing the risk of developing and dying of breast cancer.

The scatter graphs in Figure 5 demonstrate the relative risks of endometrial and breast cancer with duration of estrogen use.[72] Although there is clearly an increased risk of endometrial carcinoma, which is apparent immediately and continues to increase with duration of use, the data regarding breast cancer risk are not so explicit. At best, there is a modest elevation with duration of use. The mild to moderate rise in breast cancer risk seen in this graph has been challenged by some. Whether this represents a true rise in breast cancer risk or is an artifact of the longevity associated with HRT is not clear. Breast cancer is largely a disease of older women. Because women who use hormones do not die of the complications associated with osteoporosis or cardiovascular disease, it has been proposed that this rise in breast cancer risk may actually indicate that these women are simply living long enough to develop the breast cancer that they would have gotten anyway. Viewed from another perspective, women who do not use hormones are dying of other causes before they reach an age when their breast cancer risk increases, regardless of exogenous hormone use.

Several studies have shown no increased risk of breast cancer among menopausal women who use exogenous hormones.[73–77] The overall relative risk of breast cancer in these series ranges from 1 to 1.07. Metanalyses regarding HRT and breast cancer risk similarly demonstrate minimal or no increased relative risk of breast cancer with exogenous hormone use.[78,79]

The Nurses' Health Study is one of the largest studies of menopausal HRT. Between 1976 and 1986, questionnaires were sent to more than 121,000 female nurses. Of those who answered and for whom there were sufficient data for analysis, the study actually analyzed 354 women who never used hormones, 180 current users of hormones, and 163 past users. The authors concluded that there was no increased risk with past use or duration of use of hormones. As for current users, they found an increased relative risk of breast cancer. It has been contended that this may be a falsely elevated relative risk for several reasons. Compared with past users and never users, current users had almost twice the incidence of nulliparity and were more likely to consume alcohol (alcohol consumption was an independent risk factor for breast cancer risk in this study). They were also more likely to have "benign breast disease." Although the previously mentioned study by Dupont et al.[43] demonstrated no increased risk when women with benign breast disease used hormone therapy, critics of this study argue that these were not confirmed diagnoses by specified pathologists, therefore potentially representing misdiagnoses or *in situ* disease. Mammograms were more likely to be done in women taking hormones compared with those not taking hormones. The increased relative risk may, therefore, represent screening bias. Indeed, the women who used HRT had smaller tumors of earlier stage than women who did not use hormones, which seems to support the argument of screening bias. In addition to screening biases, however, there is some evidence that women who use estrogen develop better-differentiated tumors than women who do not used hormones.[80]

As for the subgroup of women who developed breast cancer during the follow-up period, those currently using hormones had a lower odds ratio for death than did nonusers or never users. This may be a result of the cardioprotective effect, but clearly hormone use did not result in worse survival when women who used hormones were later diagnosed with breast cancer. An important secondary finding from this study is that estrogen receptor status was not different between the group using hormones and the group not using hormones: approximately 65% were positive for estrogen receptor in both groups. This is significant because many physicians fear that hormone use will result in an alteration of hormone receptor status, which could potentially affect the ability to treat women who go on to develop breast cancer, and may even lower survival rates. The findings from this study appear to allay that fear.

So far, most studies demonstrate that the breast cancer risk, if any, is minimal in women who use hormones. The benefits of HRT may very well outweigh any theoretic risk. The greatest concern for most clinicians is whether all of these studies have a hidden bias. Women who are thought to be at high risk for breast cancer (*e.g.*, those with strong family histories) may not be well represented in these series because most physicians are reluctant to prescribe hormones to these women.

Steinberg et al.[81] performed a metanalysis of studies to address the issue of exogenous estrogen use among women with a family history of breast cancer. They reported an overall increased relative risk of 3.4 (95% CI 2 to 6) for women who used hormones and had a family history of

breast cancer *versus* women who used hormones and had no family history of breast cancer. With the identification of specific genetic aberrations, including BRCA-1 and BRCA-2, it is not clear how subgroup analysis will affect risk stratification in studies such as this. It remains to be demonstrated whether women who have a family history of breast cancer and use exogenous hormones but do not have any identifiable genetic predisposition (*e.g.*, alterations in the BRCA genes) will prove to be at an elevated relative risk for breast cancer.

Grady et al.[82] performed an interesting metanalysis to calculate estimated changes in life expectancy among women with a family history of breast cancer who use HRT *versus* those who do not. They calculated an increase from 13% to 24% in the lifetime probability that breast cancer will develop in a woman who uses estrogen and progesterone and has a family history of breast cancer *versus* a woman who has no family history and uses hormones. Despite this, the life expectancy was 83.1 years *versus* 83.8 years for the two groups. Because of the positive effects of HRT on cardiovascular health and osteoporosis risk, in this analysis there was only a minimal decrease in life expectancy for women with a family history of breast cancer who used exogenous estrogen. Data such as these add to the uncertainty in advising "high-risk" patients about HRT. Clearly, no consensus exists on the matter, and no study has been done that can conclusively address this issue, especially in light of our ever-expanding knowledge and understanding regarding the genetics of breast cancer.

Women who use HRT tend to be of a higher socioeconomic standing and have access to routine health care maintenance and follow-up, compared with women who do not use HRT. Also, women who use HRT tend to lead healthier lifestyles. Whether these women have healthier habits, such as exercising more, eating low-fat and low-cholesterol diets, and taking calcium and vitamin supplements, is not proven. These types of differences, however, may affect the data from all of the studies listed because of an independent effect in lowering cholesterol, improving cardiovascular health, and improving bone density. In addition, exercise and a low-fat diet may also lower breast cancer risk, irrespective of exogenous hormone use.[83,84] Prospective studies addressing issues such as these are underway and should clarify whether HRT influences breast cancer risk when these types of variables are controlled for.

Hormone Replacement After the Diagnosis of Breast Cancer

With all the controversy surrounding breast cancer risk among women who at baseline have no risk or a low risk for breast cancer, what do we tell women who have had breast cancer diagnosed and treated and wish HRT for the relief of menopausal symptoms? One survey, from Johns Hopkins University,[85] determined the willingness of survivors of breast cancer to take exogenous hormones for the relief of menopausal symptoms. One hundred ninety women were included in the study. Overall, one third of the women would consider HRT for the relief of menopausal symptoms despite a prior diagnosis of breast cancer. Willingness to undergo HRT was directly related to the severity of menopausal symptoms.[86]

The use of physiologic doses of exogenous hormones in survivors of breast cancer has been hotly debated for many years. Proponents of HRT in this group of women point to trials involving hormone exposure during pregnancy as well as the lack of benefit from oophorectomy. The National Surgical Adjuvant Breast Project[87] reported findings regarding oophorectomy more than 25 years ago. This trial randomized both node-negative and node-positive women into three treatment groups: bilateral oophorectomy, treatment with triethylenethiophosphoramide (thio-TEPA), and no additional treatment. There was no difference in outcome among the three groups. Given that premenopausal women with breast cancer do not routinely undergo oophorectomy and are, therefore, exposed to physiologic doses of estrogen despite the diagnosis of breast cancer, why then deny physiologic hormone replacement to menopausal women?

There are, of course, some concerns particular to the woman who has had breast cancer that are not at issue when considering HRT in other women. First is the issue of possible effects on tumor dormancy: will dormant cells be stimulated by exogenous hormones? Data from the Nurses' Health Study seem to allay this fear. That study showed improved survival among women who developed breast cancer and were using exogenous hormones. Similarly, extrapolation of data regarding the hormonal effects on breast cancers in pregnant women also seem to ally this fear, but whether this extrapolation is valid is debatable. The second question raised pertains to subgroups of breast cancer patients. Is HRT safer in some groups than in others? Does duration of time since diagnosis matter? What about other prognostic factors, such as nodal status and characteristics of the primary tumor? Finally, what does receptor status mean with respect to HRT? Is the receptor status of any potentially dormant cell the same as that of the primary tumor, and does it matter? Approximately 20% of estrogen receptor-negative tumors do respond to hormonal manipulation, whereas 25% of estrogen receptor-positive tumors do not. Evidently, there are influences other than estrogen on tumor growth. The complex interactions between factors may be more important than, or may even override, any one factor, including estrogen.

Several studies have compared the disease-free survival among patients with breast cancer who used hormones with those who did not.[88–92] There was no difference in disease-free survival among the groups. If it were true that HRT could activate dormant breast cancer cells, then women using exogenous hormones at the time of breast cancer diagnosis should have a worse prognosis than women not using hormones. Most studies do not support this theory and

have demonstrated, instead, an improvement in survival among hormone users. These data argue against the concern regarding tumor dormancy and aggressiveness of metastatic potential.

Stoll[93] attempted to address the issue of recurrence and HRT. Although the study was small and had a follow-up of only 2 years, the author found no recurrences in patients using HRT. Because most recurrences of breast cancer appear in the first 2 years, this study has shown at least no acceleration of recurrence when hormones are used by women previously diagnosed with and treated for breast cancer. A series by Wile et al.[94] followed 25 women with *in situ* to stage III disease treated with HRT for 2 to almost 7 years and found that the recurrence rate was similar to that of control patients. This study suggested that HRT has no adverse effects in women who have had breast cancer. Interestingly, patients who did have recurrence had started HRT within 2 years of the breast cancer diagnosis. Whether the timing of hormone replacement is important, or whether these represent recurrences that would have taken place anyway, is not clear.

Several studies have addressed the concern about accelerated tumor growth in women with breast cancer who wish to use HRT. One moderately sized series by Gambrell[95] looked at 256 women and assessed mortality rate and nodal status among those using hormones versus those not using hormones. Survival was better in the group using HRT than in the group not using HRT. This may have been a result of the cardioprotective effects of hormones. In response to exogenous hormone use, however, at least there was no increased mortality rate in this group, suggesting no acceleration of tumor growth. As for nodal status and risk for metastatic disease, women who used hormones had a lower incidence of positive nodes than did nonusers of hormones. This finding suggests that the metastatic potential of breast tumors is not augmented by the addition of hormones. Among node-negative women, the death rate was significantly lower in those who used hormones than in those who did not. This may also represent the cardioprotective effects of estrogens, but it also demonstrates no increased rate of death among hormone users, arguing against the concern about acceleration of tumor growth in patients with breast cancer who use hormones.

In a smaller study by Stoll,[96,97] 65 women with advanced breast cancer and postmenopausal symptoms were treated with HRT. All had measurable soft-tissue metastases. Not only was there no acceleration of tumor growth in response to exogenous hormones, but there was an objective remission of metastases in 22% of the women. Findings such as this point to interactions much more complex than the simplistic view of estrogen-induced proliferation in breast cells.

Bergkvist et al.[98] studied 261 patients with breast cancer and found that both relative and observed survival rates were better in women who used HRT than in those who did not. Similar results were achieved by Strickland et al.[89] There was a statistically significant improvement in survival among women with breast cancer who used hormones compared with those who either never used hormones or who had used them in the past. Data from that series demonstrate that the duration of HRT does not appear to affect survival statistics: women who used hormones for longer periods of time had survivals similar to women who used hormones for a short period of time or not at all.

To reach a consensus on this matter, the Eastern Cooperative Group Breast Cancer Committee[99] performed a meta-analysis of studies regarding the issue of HRT in survivors of breast cancer. The members were careful to state that at present the standard of care is to discourage the use of HRT in these women. They then went on to ask if it was perhaps time for a change, and questioned whether this standard was justified, based on quality of life and lack of data to support the current standard. They raised concerns regarding the issue of a woman surviving her breast cancer only to succumb to cardiovascular disease, or to suffer severe menopausal symptoms. Although they reached no consensus, they tended toward changing the dictum of discouraging the use of hormones in survivors of breast cancer.

Table 2. ALTERNATIVES TO HORMONE REPLACEMENT THERAPY

Medroxy progesterone acetate, megesterone acetate
Weight gain
Mastodynia
Galactorrhea
Clonidine, bromocriptine, nalaxone
High doses required
Side effects
Veralipride
Dopamine agonist
Modest estrogenic effect

Alternatives to Hormone Replacement

Because of the theoretic risks and concerns regarding HRT, alternatives have been sought. Table 2 lists several alternative pharmacologic therapies, but they have only a modest effect on menopausal symptoms. In addition to the medications listed, new synthetic estrogens are under investigation. Some women have tried "natural" remedies to relieve the symptoms of menopause; most commonly used are herbs and herbal teas such as ginseng. Although ginseng does contain estrogen, the amount ingested while taking herbs and teas is variable, and its effectiveness in treating menopausal symptoms has not been studied in a controlled manner. Vitamin E has also been used by some with vague success.

In addition to alternative drugs, alternative routes of administration of estrogen have been sought. Contrary to popular belief, transvaginal estrogen is well absorbed and does produce systemic levels and systemic effects.[100] Eu-

ropean studies have shown that low doses can be used without producing significant increases in systemic levels but still providing good control of urogenital symptoms.[101] Daily administration is required until the vaginal mucosa is restored, at which time biweekly administration is sufficient to maintain the effect. Unfortunately, these low-dose preparations are not available in the United States.

Role of Tamoxifen

With the increasing use of tamoxifen to treat breast cancer, attention has focused on its potential to relieve menopausal symptoms as well as prevent and treat cardiovascular disease and osteoporosis. The Scottish Cancer Trial[102] demonstrated a 50% reduction in the rate of myocardial infarction among women who took tamoxifen compared with those who did not. Similarly, the Stockholm Trial[103] demonstrated decreased hospital admissions for cardiac disease among women who used tamoxifen compared with those who did not. The estrogenic effects of tamoxifen include improvement of the lipid profile and maintenance of bone density, although its degree of protection does not appear to be equivalent to that of estrogen.[104–109] In addition, the benefits of its antiestrogenic qualities can be used, with a possible decreased risk of contralateral breast cancer. Unfortunately, these antiestrogenic effects include worsening of menopausal symptoms: up to 25% of women complain of worsening hot flashes while using tamoxifen.

Combination therapy with tamoxifen and estrogen has been suggested recently and is being investigated. The hope is to obtain the benefits of both while counterbalancing the disadvantages of each. There are concerns regarding a possible synergistic enhancement of cancer risk when tamoxifen and estrogen are combined, especially in light of evidence to suggest that tamoxifen stimulates estrogen secretion in premenopausal women.[110–112] So far, it appears that the risk for endometrial cancer can be countered by the addition of progesterone to the estrogen replacement regimen. To bolster the theory about the potential benefit of combining tamoxifen with estrogen, the results of the National Surgical Adjuvant Breast Project Trial B14[113] have been extrapolated. That trial revealed that premenopausal women with node-negative, estrogen receptor-positive breast cancers derived greater benefit from tamoxifen therapy than did postmenopausal women with similar tumors and stage of disease. However, whether this beneficial effect was the result of an estrogen–tamoxifen interaction is not obvious, and, indeed, has not been studied.

There are no published *in vitro* studies on the effects on growth factors and tumor growth when these two drugs are used in combination. It is interesting that the effects of both antiestrogen and estrogen therapy last approximately 12 months. In culture, estrogen both stimulates and inhibits breast cell growth. The differential response is dose-dependent; low doses of estrogen stimulate cell growth, and high doses inhibit growth.[114] Tamoxifen therapy results in a 50% response rate for estrogen receptor-positive tumors; this figure can reach 75% if the estrogen receptor concentration exceeds 100 fmol/mg of cytosolic protein.[115] However, treatment with 10 mg conjugated estrogens three times per day produces a 30% response rate overall in postmenopausal women with metastatic breast cancer. One must use caution in interpreting data such as these.

The use of tamoxifen with high-dose estrogen to treat the symptoms of menopause in addition to cardiovascular disease and osteoporosis, as well as to incur an additive inhibitory effect on breast tumor growth, would represent a great leap of faith with no data to support the theory. The optimal dose of estrogen for women with breast cancer, particularly the optimal dose of estrogen when used in combination with tamoxifen, has not been studied. Two clinical studies have demonstrated relief of menopausal symptoms using tamoxifen in conjunction with estrogen replacement. No adverse effects in terms of rate of metastases, recurrence, or decreased survival rates were demonstrated. Similar studies have confirmed no adverse effects when estrogen was added to tamoxifen therapy. However, all studies were small and had limited follow-up.

Summary

Most data demonstrate that breast cancer is hormonally influenced. For the woman with no history of breast cancer, the benefits of HRT may outweigh the risks. Although it remains the standard of care to discourage hormone use in patients who have had breast cancer, future studies may result in a change of this standard. There needs to be more research into these complex hormonal interactions so that we will have a better understanding of the true risks and benefits when we attempt to advise our patients regarding the best treatment regimens for them.

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